87519-25-3; **8** methiodide, 87519-26-4; **9**, 38609-44-8; **9** THP ether, 87519-27-5; **10**, 37905-04-7; **11**, 87519-28-6; **12**, 87519-29-7; **13**, 60274-60-4; **14**, 78592-82-2; **15**, 87519-30-0; **16**, 87519-31-1; (*R,S*)-**17**, 87519-32-2; (*S*)-**17**, 87583-39-9; (*R*)-**17**, 87583-40-2; (*R,S*)-**18**, 87519-33-3; (*S*)-**19**, 87519-34-4; (*S*)-**20**, 87519-35-5; (*R*)-**20**, 87519-36-6; **21**, 87519-37-7; **21** methyl ester, 87519-38-8; (*R,S*)-**22**, 87519-39-9; (*S*)-**22**, 87583-41-3; (*R*)-**22**, 87583-42-4; (*R*)-**22** methyl ester, 87519-40-2; (*S*)-**23**, 87519-41-3; (*R*)-**23**, 87519-42-4; (*R*)-**23** methyl ester, 87519-43-5; (*R,S*)-**24**, 87519-44-6; (*R,S*)-**24** methyl ester, 87519-45-7; (*S*)-**24**, 87583-43-5; (*S*)-**24** methyl ester, 87583-44-6; (*R*)-**24**, 87583-45-7; (phenylthio)acetyl chloride, 7031-27-8; geraniol, 106-24-1; 3,7-dimethyl-2(*E*),5(*E*),7-octatrienyl (phenylthio)acetate, 87519-46-8; 2,4,4-trimethyl-2-oxazoline, 1772-43-6; geranyl acetate, 105-87-3; 2,6-dimethyl-8-hydroxy-2-(*E*),6(*E*)-octadien-1-ol, 26488-97-1; 8-acetoxy-2,6-dimethyl-2-(*E*),6(*E*)-octadien-1-ol, 37905-03-6; diethyl malonate, 105-53-3; 3-butyn-1-ol, 927-74-2; (*R,S*)-propylene oxide, 16033-71-9; (*S*)-propylene oxide, 16088-62-3; (*R*)-propylene oxide, 15448-47-2.

Studies on the Nactins: Total Synthesis of (±)-*tert*-Butyl 8-*O*-(*tert*-Butyldimethylsilyl)nonactate

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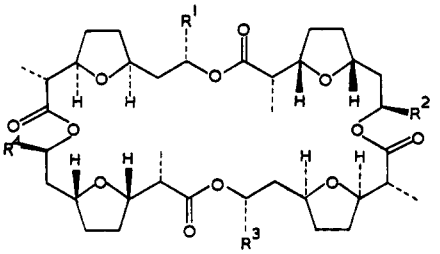
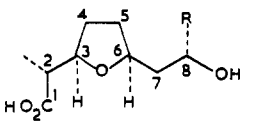
The title nonactic acid derivative (**32**) was prepared in racemic form from 2,3,5-tri-*O*-acetyl-γ-D-ribonolactone (**17**). Lactone **17** reacted with DBU to give 3-acetoxy-5-methylene-2,5-dihydrofuran-2-one (**18**), which on hydrogenation over $Pd/CaCO_3$ stereoselectively (>97:3) gave 3[*R*(*S*)]-acetoxy-5[*S*(*R*)]-methyltetrahydrofuran-2-one (**16a**). Reaction of this with diisobutylaluminum hydride, $EtO_2CCH{=}PPh_3$, hydrogen over Rh/Al_2O_3, CF_3CO_2H, and *t*-$BuMe_2SiCl$ in sequence gave 5*S*(*R*)-[2[*S*(*R*)]-[(*tert*-butyldimethylsilyl)oxy]propyl]tetrahydrofuran-2-one (**30b**). Subsequent condensation with *tert*-butyl 2-lithiopropanoate gave, on acidification and hydrogenation over Rh/Al_2O_3, **32**, which was formed with an 85:15 diastereoselectivity. Alternative but less concise routes to **16a** were explored. In addition, unsuccessful attempts to prepare nonactic acid (**2a**) from *threo*-pentanetriol (**21a**) were examined.

The nactins **1** are a group of macrotetrolide antibiotics produced by *Streptomyces* sp.[2] These are neutral ionophores noted for the ability to mediate cation transport. In particular, nonactin (**1a**) is especially effective in con-



1 a $R^1=R^2=R^3=R^4=Me$
b $R^1=Et$, $R^2=R^3=R^4=Me$
c $R^1=R^3=Et$, $R^2=R^4=Me$
d $R^1=R^2=R^3=Et$, $R^4=Me$
e $R^1=R^2=R^3=R^4=Et$



2 a R = Me
b R = Et

trolling mitochondrial potassium ion flux. All the nactins **1** consist of four hydroxy acids, either nonactic acid **2a** or **2b**, linked to produce a 32-membered tetralactone ring. Nonactin (**1a**) is a meso compound since the alternating hydroxy acid subunits (**2a**) are of opposite absolute stereochemistry. Thus, hydrolysis of **1a** produces racemic **2a**.[2,3] Monactin (**1b**), dinactin (**1c**), trinactin (**1d**), and tetranactin (**1e**) are homologues of **1a** containing an increasing ratio of **2b**:**2a**. Clearly the nactins **1** are both stereochemically and biosynthetically[4] intriguing.

Nonactic acid (**2a**) has been the subject of extensive synthetic studies. Introduction of the cis stereochemistry at the tetrahydrofuran ring (C-3 and C-6) is easiest to achieve. Thus, either catalytic hydrogenation[5] of, or oxyallyl cycloaddition to,[6] suitably functionalized furans has been widely exploited in nonactic acid (**2a**) synthesis. Alternative approaches by Ireland[7] and Fraser-Reid[8] have used carbohydrates as precursors to both antipodes of **2a**. Both Gerlach[9] and Bartlett[10] have prepared racemic **2a** from acyclic precursors, namely, 7-octene-2,4-dione and 1,7-octadien-4-ol, respectively. With the sole exception of Bartlett's elegant studies,[10] all total syntheses of **2a** have not adequately controlled the stereochemistry at both the extracyclic centers (C-2 and C-8). Bartlett employed both phosphate extension methodology, converting **3** to **4**, and steric approach directed hydrogenation, in transforming **5** into **6**, in the synthesis of (±)-**2a**. Herein we report

(1) Present address: Department of Chemistry, Northwestern University, Evanston, IL 60201.
(2) Westley, J. W. *Adv. Appl. Microbiol.* **1977**, *22*, 177. Gerlach, H.; Prelog, V. *Justus Liebigs Ann. Chem.* **1963**, *669*, 121. Dominguez, J.; Dunitz, J. D.; Gerlach, H.; Prelog, V. *Helv. Chim. Acta* **1962**, *45*, 129.
(3) All structures refer to racemic modification with the exception of **17**.
(4) Pape, H. *Arch. Mikrobiol.* **1972**, *82*, 254. Ashworth, D. M.; Robinson, J. A.; Turner, D. L. *J. Chem. Soc., Chem. Commun.* **1982**, 491.
(5) For summary, see: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3.
(6) Arco, M. J.; Trammell, M. H.; White, J. D. *J. Org. Chem.* **1976**, *41*, 2075.
(7) Ireland, R. E.; Ververt, J. P. *Can. J. Chem.* **1981**, *59*, 572.
(8) Sun, K. M.; Fraser-Reid, B. *Can. J. Chem.* **1980**, *58*, 2732.
(9) Gerlach, H.; Wetter, H. *Helv. Chim. Acta* **1974**, *57*, 2306.
(10) Bartlett, P. A.; Jernstedt, K. K. *Tetrahedron Lett.* **1980**, 1607.

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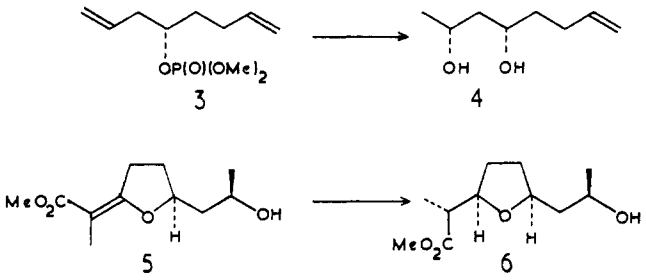
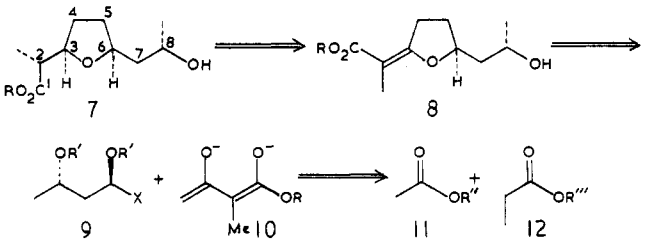
details of our stereocontrolled total synthesis of a derivative of (±)-nonactic acid (**2a**).[11]



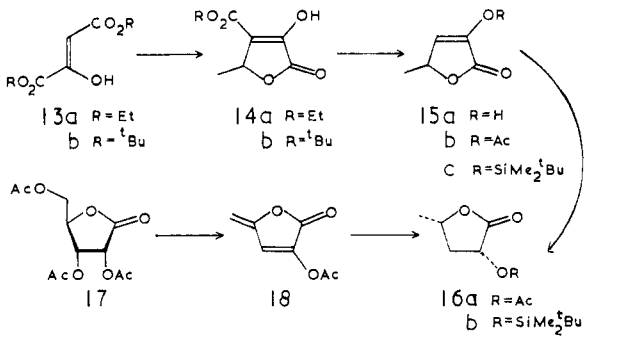
Results and Discussion

On the basis of Bartlett's observations, we were certain that the steric approach controlled hydrogenation of the α,β-unsaturated ester **8** should conveniently provide **7** and thus nonactic acid (**2a**). Ester **8** should be readily available from dianion **10** and the electrophile **9**. This strategy



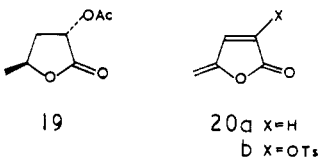
should be highly flexible. First, **9** could be used at the triol (X = CH_2OTs, etc.), aldehyde (X = CHO), or acid (X = CO_2R'') oxidation level. Second, dianion **10** has as synthetic equivalents esters **11** and **12**, which are linked via early or late cross-Claisen condensation reactions. Thus control of the relative stereochemistry at C-6 and C-8 (nonactic acid numbering) in preparing **9** should ensure the correct stereochemistry in a synthesis of **2a**.

Preparation of Lactone 16a. As a key intermediate for the preparation of **9**, we sought a concise route to lactone **16a**. In 1950, Rossi and co-workers reported that the butenolide **15b** was smoothly hydrogenated over palladium on calcium carbonate to produce a single dihydro derivative.[12] Although these authors did not determine the stereochemistry of their product, we were certain this was lactone **16a**. Ollis and others[13] have noted the excellent cis diastereoselection on the catalytic hydrogenation of related butenolides. Thus we initially repeated the Rossi synthesis. The cross-Claisen condensation of diethyl oxalate and ethyl acetate gave **13a**, which reacted with acetaldehyde to produce **14a**. On heating in hydrochloric



and acetic acids, **14a** underwent hydrolysis and decarboxylation to produce the enol (**15a**). However, in our hands, the conversion of **14a** into **15a** was both slow and low yielding. To facilitate this synthesis, we repeated the sequence from di-*tert*-butyl oxalate and *tert*-butyl acetate. Unlike **14a**, ester **14b** was rapidly hydrolyzed and decarboxylated in acid solution, giving **15a** (72%). As described by Rossi,[12] **15a** was acetylated by using acetyl chloride and pyridine and the derived enol acetate **15b** was hydrogenated over palladium on calcium carbonate in ethanol solution. The product dihydro derivative **16a** (98%) was obtained as a single diastereoisomer. The NMR spectrum of this was fully consistent only with cis stereochemistry. Daremon et al.[14] have reported the NMR spectra of both **16a** and **19**. It is ironic that these authors speculated as to the Rossi compound being *trans*-**19**, not **16a**; their own spectra refute this suggestion. We also prepared a mixture of **16a** and **19** (55:45) from 3-hydroxybutanal via 2,4-dihydroxypentanenitrile, acidic hydrolysis,[15] and acetylation.[14] Comparison of data showed that **16a** prepared from **15b** was at least 97:3 diastereoisomerically pure. Enol **15a** was also converted into the *tert*-butyldimethylsilyl ether **15c** (53%). This was hydrogenated over palladium on calcium carbonate to give **16b** (82%). Again the product was formed with excellent diastereoselectivity (>97:3).

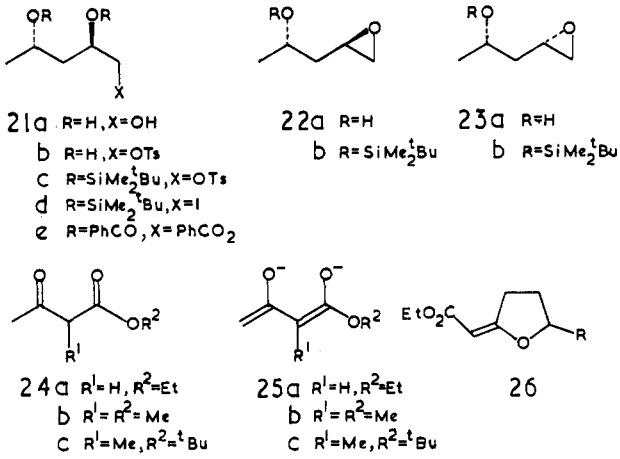
Although we had a highly stereoselective route to **16a**, we were concerned that this was too lengthy and inelegant. Thus we sought a more concise route. On reaction with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[16] in THF 2,3,5-tri-*O*-acetyl-D-ribonolactone (**17**) gave the doubly eliminated methylenebutenolide **18** (94%). The destruction of the chirality of **17** was not a chemical heresy since we sought a route to racemic nonactic acid (**2a**). In contrast



to protoanemonin (**20a**),[17] the butenolide **18** is both crystalline and stable. Recently Barton has reported **20b** as a byproduct formed during the partial 2,5-di-*O*-toluene-4-sulfonylation of γ-ribonolactone.[18] On hydrogenation over palladium on calcium carbonate, **18** was smoothly converted into **16a** (90%). The NMR spectrum of the product showed the absence (<3%) of the trans diastereoisomer (**19**).

Attempted Preparation of Nonactic Acid (2a) via Triol 21a. Lactone **16a** was reduced by lithium aluminum hydride (72%) or more efficiently by sodium borohydride (100%) to produce *threo*-1,2,4-pentanetriol (**21a**). Both the ^{13}C and ^1H NMR spectra of this material were consistent with diastereoisomeric purity.[19] On reaction with *p*-tolylsulfonyl chloride, the primary hydroxyl group was selectively transformed to give **21b** (60%). This monotosylate (**21b**) was *tert*-butyldimethylsilylated, giving **21c** (93%), and subsequently reacted with magnesium iodide in diethyl ether to produce the iodide **21d** (70%). In addition, reaction of tosylate **21b** with DBU gave the corre-

(11) Barrett, A. G. M.; Sheth, H. G. *J. Chem. Soc., Chem. Commun.* **1982**, 170.
(12) Rossi, A.; Schinz, H. *Helv. Chim. Acta* **1948**, *31*, 473. Fleck, F.; Rossi, A.; Hindler, M.; Schinz, H. *Ibid.* **1950**, *33*, 130.
(13) Hussain, S. A. M. T.; Ollis, W. D.; Smith, C.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans 1* **1975**, 1480.
(14) Daremon, C.; Rambaud, R.; Verniette, M. *C. R. Hebd. Seances. Acad. Sci.* **1971**, *273*, 1273.
(15) Gudgeon, H.; Hill, R.; Isaacs, E. *J. Chem. Soc.* **1951**, 1926. Drell, W.; Dunn, M. S. *J. Am. Chem. Soc.* **1948**, *70*, 2057.
(16) Timpe, W.; Dax, K.; Wolf, N.; Weidmann, H. *Carbohydr. Res.* **1975**, *39*, 53.
(17) Asahina, Y.; Fujita, A. *J. Pharm. Sci. Jpn.* **1920**, *455*, 1.
(18) Barton, D. H. R.; Bénéchie, M.; Khuong-Huu, F.; Potier, P.; Reyna-Pinedo, V. *Tetrahedron Lett.* **1982**, *23*, 651.
(19) Hartmann, F. C.; Barker, R. *J. Org. Chem.* **1964**, *29*, 873.

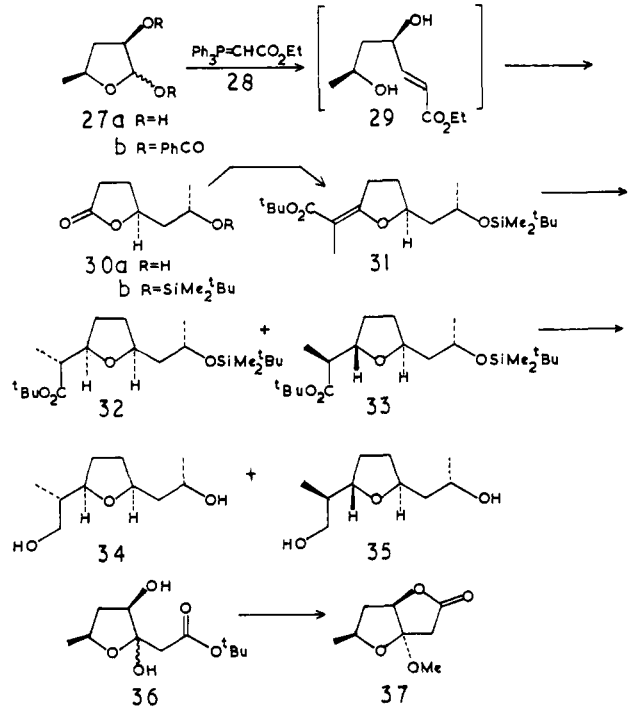


sponding epoxide **22a**[20] (46%), which was protected (92%) to produce **22b**. As a model system for **22b**, 1-penten-4-ol was epoxidized[21] and *tert*-butyldimethylsilylated to give the erythro–threo mixture **22b** and **23b**.

β-Keto esters including **24** on reaction with base, for example, sodium hydride and *n*-butyllithium in sequence, produce the corresponding dianions **25**. These have been extensively studied by Harris, Weiler, and others,[22] since they are rapidly functionalized by electrophoresis (alkyl halides, aldehydes, ketones, and esters) at the terminal carbon. Thus we attempted to condense **25** and **21c**, **21d**, and the **22b**, **23b** mixture. Although we extensively varied the countercation (Li, Na, Me_3Si), solvent (THF, 1,2-dimethoxyethane), temperature (−78 to 40 °C), or additive (HMPT, CuI or PhSCu), no substitution products could be detected. Bryson[23] has reported that simple epoxides react with **25a** to produce the tetrahydrofuran derivatives **26**. Although we are able to repeat Bryson's reactions, the epoxide mixture (**22b** and **23b**) is of dramatically lower reactivity. We therefore abandoned this route to nonactic acid (**2a**).

Preparation of Nonactic Acid Derivative 32. Since we were unable to condense electrophiles derived from triol **21a** with dianions **25**, we examined the lactol **27** as precursor to **2a**. Lactone **16a** was reduced by using diisobutylaluminum hydride in toluene solution to produce **27a** (85%). Moffatt has reported numerous examples of the condensation of stabilized ylides with furanose derivatives.[24] Thus **27a**, as expected, reacted with ylide **28**. The intermediate, presumably **29**, was not isolated but was directly hydrogenated over rhodium on alumina to give, on acidification, lactone **30a** (60%) after distillation. Alternatively, after lactonization, the crude **30a** was *tert*-butyldimethylsilylated and the product **30b** (55%) isolated by chromatography.

Although the cross-Claisen condensation reaction has been extensively investigated, the reaction of ester enolates with lactones has been less widely studied.[25] *tert*-Butyl propanoate was metalated with lithium diisopropylamide and the resulting enolate added to **30b**. Workup via acidification gave **31** exclusively as the *E* geometric isomer. Bryson has demonstrated that the *E* geometry in simple tetrahydrofurylideneacetate esters (**26**) is more stable than



the *Z*.[26] Ester **31** contained all the carbon atoms required for nonactic acid (**2a**), thus hydrogenation over rhodium on alumina slowly gave **32**. High-resolution NMR spectroscopy showed that this material (**32**) was contaminated with the diastereoisomer **33** (85:15). Thus the selectivity of hydrogenation is identical with Bartlett's precedent.[10]

The major diastereoisomer **32** was authenticated as follows: reduction with lithium aluminum hydride followed by acidification gave diol **34** accompanied by the minor diol **35**. Nonactin[6] was likewise reduced to produce **34**. Both synthetic and natural materials were identical.

Claisen Condensation of Lactone 16a. We briefly examined the carbon skeleton homologation of lactone **16a** as a route to **2a**. Lactone **16a** was reacted with the enolate of *tert*-butyl acetate to give cross-Claisen condensation product **36** as a mixture of diastereoisomers (63%). This reacted with methanol and trifluoroacetic acid to give **37** (54%). In principle, either **36** or **37** should be available for further transformation toward **2a**. Since we succeeded in preparing **32** via **27** this was not carried out.

Conclusion. We have completed the total synthesis of the (±)-nonactic acid derivative **32** from **17** using the concise strategy via **18**, **16a**, **27a**, **30b**, and **31**. Introduction of the correct stereochemistry was ensured with the use of two steric approach controlled hydrogenations (**18** to **16a** and **31** to **32**).

Experimental Section

General Procedures. Reactions were carried out under dry N_2 at room temperature unless otherwise stated. Low reaction temperatures were recorded as bath temperatures. *n*-BuLi in hexane or diisobutylaluminum hydride in PhMe was added dropwise over 10 min. All solvents and reagents were purified by standard means.[27] THF was freshly redistilled from potassium benzophenone ketyl under argon. Organic extracts were dried over Na_2SO_4 or $MgSO_4$, filtered, and rotary evaporated at ≤50 °C; involatile compounds were further evaporated at <2 mmHg. Chromatography refers to flash chromatography[28] on Merck Kieselgel H. Samples for combustion analysis were purified either

(20) For a related transformation of **21b**, see ref 19.
(21) Yanko, W. H.; Mosher, H. S.; Whitmore, F. C. *J. Am. Chem. Soc.* **1945**, *67*, 666.
(22) For examples, see: Weiler, L. F. *J. Am. Chem. Soc.* **1970**, *92*, 6707. Harris, T. M.; Harris, C. M. *Org. React. (N.Y.)* **1969**, *17*, 177.
(23) Bryson, T. A. *J. Org. Chem.* **1973**, *38*, 3428.
(24) For example, see: Ohrui, H.; Jones, G. H.; Moffatt, J. G.; Madox, M. L.; Christensen, A. T.; Byram, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602.
(25) For example, see: Duggan, A. J.; Adams, M. A.; Brynes, P. J.; Meinwald, J. *Tetrahedron Lett.* **1978**, 4323.
(26) Krueger, S. A.; Bryson, T. A. *J. Org. Chem.* **1974**, *39*, 3167.
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(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

via distillation or, where boiling points are not specified, via rechromatography with rotary evaporation (<40 °C) of the appropriate fractions and further evaporation (0.1 mmHg) overnight. Melting points were determined on a Kofler hot stage apparatus and are not corrected. Unless stated to the contrary, IR spectra were recorded as Nujol mulls (solids) or films (oils), UV spectra in EtOH, and NMR spectra in $CDCl_3$ with Me_4Si as internal reference.

3[*R*(*S*)]-Acetoxy-5[*S*(*R*)]-methyltetrahydrofuran-2-one (16a). 3-Acetoxy-5-methyl-2,5-dihydrofuran-2-one (**15b**,[12] 20.34 g) and Pd on $CaCO_3$ (2%, 8.7 g) in EtOH (330 mL) were hydrogenated at 1 atm for 24 h and filtered, and the catalyst was leached with more EtOH. The combined filtrate and washings were evaporated to give **16a**[12] (20.2 g, 98%) as a colorless oil: bp 80–81 °C (0.1 mmHg); IR 1790, 1750, 1380, 1240–1200 cm^{-1}; NMR (250 MHz) δ 1.50 (d, 3 H, J = 6.5 Hz), 1.90 (dt, 1 H, J = 13.2, 10.8 Hz), 2.16 (s, 3 H), 2.84 (ddd, 1 H, J = 13.2, 8.6, 5.7 Hz), 4.6 (m, 1 H), 5.54 (dd, 1 H, J = 10.8, 8.6 Hz); mass spectrum, m/e 158 ($M^{+\cdot}$), 72 (base).

Di-*tert*-Butyl 2-Hydroxy-2-butene-1,4-dioate (13b). To a stirred suspension of KO-*t*-Bu (7.06 g) in Et_2O (50 mL) under nitrogen at 0 °C was added di-*tert*-butyl oxalate (12.12 g) and *tert*-butyl acetate (6.96 g) in Et_2O (50 mL). On completion of the addition, the solution was refluxed (3 h), cooled, and quenched with dilute hydrochloric acid and ice. The ether layer was dried and evaporated to give **13b** (11.5 g, 79%) as a white solid: mp 74–76 °C; IR 1725, 1650, 1285, 1245, 1155 cm^{-1}; NMR (60 MHz) δ 1.5 (s, 9 H), 1.55 (s, 9 H); mass spectrum, m/e 245, 244 ($M^{+\cdot}$), 57 (base). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.13; H, 8.29.

4-[(*tert*-Butyloxy)carbonyl]-3-hydroxy-5-methyl-2,5-dihydrofuran-2-one (14b). NaH (100%, 1.03 g) and CH_3CHO (2.85 g) were added in sequence to **13b** (10.5 g) in THF (50 mL), and the mixture was heated at 50 °C for 6 h. After evaporation, concentrated hydrochloric acid, ice, and Et_2O were added to the residue. Evaporation gave crude **14b** (8.7 g, 95%) as a yellow oil, which was used without further purification: IR 3400, 1780, 1720, and 1655 cm^{-1}; mass spectrum, m/e 214 ($M^{+\cdot}$), 199, 113, 57 (base).

3-Hydroxy-5-methyl-2,5-dihydrofuran-2-one (15a). Lactone **14b** (1.0 g), CF_3CO_2H (5 mL), and Amberlite IR120H resin (0.1 g) in THF (5 mL) and water (5 mL) were stirred for 2 days at room temperature and 12 h at reflux. After filtration, the solution was evaporated and the residue chromatographed (petroleum ether–CH_2Cl_2 gradient 1:1–0:1) to give **15a** (0.38 g, 72%) as a pale yellow solid: mp 68–70 °C (benzene) (lit.[12] mp 70–73 °C).

3[*R*(*S*)]-[(*tert*-Butyldimethylsilyl)oxy]-5[*S*(*R*)]-methyltetrahydrofuran-2-one (16b). *tert*-Butyldimethylsilylation of **15a** and chromatography (petroleum ether–CH_2Cl_2 gradient 1:0–0:1) gave crude **15c** (0.85 g, 53%) as a pale yellow oil: IR 1770, 1660, 1470, 1310, 1260, 910, 850, 790 cm^{-1}; NMR (60 MHz) δ 0.15 (s, 6 H), 0.9 (s, 9 H), 1.35 (d, 3 H, J = 6 Hz), 4.85–5.15 (m, 1 H), 6.16 (d, 1 H, J = 2 Hz); mass spectrum, m/e $M^{+\cdot}$ undetected, 213, 171. Pd on $CaCO_3$ (2%, 0.5 g) was added to lactone **15c** (0.70 g) in EtOH (25 mL), and the mixture was hydrogenated at atmospheric pressure for 48 h. Filtration and evaporation gave **16b** (0.58 g, 82%) as a colorless liquid: bp 140 °C (2 mmHg); IR 1780, 1460, 1150, 1050, 1010, 780 cm^{-1}; NMR (60 MHz) δ 0.10 (s, 6 H), 0.98 (s, 9 H), 1.48 (d, 3 H, J = 6 Hz), 1.7–2.14 (m, 1 H), 2.34–2.9 (m, 1 H), 4.5 (dd, 1 H, J = 10, 8 Hz); mass spectrum, m/e $M^{+\cdot}$ absent, 215, 173. Anal. Calcd for $C_{11}H_{22}O_3Si$: C, 57.35; H, 9.63. Found: C, 57.59; H, 9.70.

3-Acetoxy-5-methylene-2,5-dihydrofuran-2-one (18). 1,8-Diazabicyclo[5.4.0]undec-7-ene (4.9 mL) was added dropwise with stirring over 20 min to 2,3,5-tri-*O*-acetyl-D-ribonic acid γ-lactone (**17**, 8.0 g) in THF (100 mL) at −20 °C under nitrogen. After 3 h at −20 °C and 2 h at room temperature, the mixture was added to ice–hydrochloric acid and Et_2O. The organic phase was dried and evaporated, and the residue was chromatographed (petroleum ether–CH_2Cl_2 gradient 1:0–0:1) to give **18** (4.3, 94%) as a white crystalline solid: mp 75–76 °C; IR ($CHCl_3$) 1785, 1740, 1645, 760 cm^{-1}; NMR (60 MHz) δ 2.32 (s, 3 H), 4.94 (d, 1 H, J = 2 Hz), 5.25 (d, 1 H, J = 2 Hz), 7.3 (s, 1 H); mass spectrum, m/e 154 ($M^{+\cdot}$), 43 (base). Anal. Calcd for $C_7H_6O_4$: C, 54.55; H, 3.92. Found: C, 54.27; H, 3.92.

3[*R*(*S*)]-Acetoxy-5[*S*(*R*)]-methyltetrahydrofuran-2-one (16a). Lactone **18** (0.344 g), Pd on $CaCO_3$ (2%, 0.2 g), and EtOH (25 mL) were hydrogenated at atmospheric pressure for 6 h. The catalyst was filtered off through Celite, and the solids were leached with more EtOH. The combined filtrate and washings were evaporated, and the residue was chromatographed (petroleum ether–CH_2Cl_2 gradient 9:1–0:1) to give **16a** (0.316 g, 90%), identical with authetic material.

Pentane-1,2[*R*(*S*)],4[*S*(*R*)]-triol (21a). Method A. Lactone **16a** (0.84 g) in THF (30 mL) was added over 20 min with stirring to $LiAlH_4$ (0.475 g) in THF (20 mL) under nitrogen at 0 °C. After 4 days, excess reagent was quenched by the dropwise addition of saturated aqueous Na_2SO_4. Anhydrous Na_2SO_4 was added, and the solids were filtered off and leached with more THF. The combined filtrate and washings were refiltered through silica and evaporated to give **21a** as a colorless oil (0.48 g, 72%): IR 3400 (br) cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 1.35 (d, 3 H, J = 6.5 Hz), 2.62–2.75 (m, 2 H), 3.55–3.8 (m, 2 H), 3.92–4.05 (m, 1 H), 4.15 (m, 1 H); ^{13}C NMR (D_2O) δ 71.6, 68.6, 67.2, 44.0, 25.5. Benzoylation (PhCOCl, pyridine, CH_2Cl_2) of an aliquot gave tribenzoate **21e** as a colorless oil. Anal. Calcd for $C_{26}H_{24}O_6$: C, 72.21; H, 5.59. Found: C, 72.11; H, 5.68.

Method B. To a stirred mixture of boric acid (1.96 g), Amberlite IR 120H resin (25 mL), and lactone **16a** (10.0 g) in water (120 mL) was added $NaBH_4$ (14.4 g) in four portions, with 0.5 h between additions. After complete addition, the pH was adjusted to 9–10 with aqueous NaOH and the mixture stirred overnight at room temperature. Amberlite IR120H resin was added to pH 7, the mixture filtered, and the filtrate evaporated. The resultant syrup was dissolved in MeOH and reevaporated. This dissolution in MeOH and reevaporation was repeated to constant weight to leave **21a** (7.6 g, 100%) identical with the previous sample.

1-[(*p*-Tolylsulfonyl)oxy]pentane-2[*R*(*S*)],4[*S*(*R*)]-diol (21b). Toluene-4-sulfonylation of **21a** in pyridine and $CHCl_3$ at 0 °C for 4 days and chromatography (petroleum ether–Et_2O gradient 1:0–1:1) gave the pure monotoluene-4-sulfonate **21b** (1.5 g, 60%) as a white crystalline solid: mp 36–39 °C; IR 3370, 825, 670 cm^{-1}; NMR (60 MHz) δ 1.2 (d, 3 H, J = 6.5 Hz), 1.45–1.65 (m, 2 H), 2.45 (s, 3 H), 3.5 (m, 2 H), 3.8–4.0 (m, 2 H), 4.2 (br s, 2 H), 7.35 and 7.82 (AB q, 4 H, J = 8.6 Hz); mass spectrum m/e $M^{+\cdot}$ weak, 244, 172 (base). Anal. Calcd for $C_{12}H_{18}O_5S$: C, 52.54; H, 6.61. Found: C, 52.25; H, 6.68.

2[*R*(*S*)],4[*S*(*R*)]-Bis[(*tert*-butyldimethylsilyl)oxy]-1-[(*p*-tolylsulfonyl)oxy]pentane (21c). *tert*-Butyldimethylsilylation of **21b** gave **21c** (6.8 g, 93%) as a colorless oil: IR 1605, 1460, 1370, 1255, 970, 850, 780, 670 cm^{-1}; NMR (250 MHz) δ 0.02 (2 s, 12 H), 0.82 (2 s, 18 H), 1.10 (d, 3 H, J = 6 Hz), 1.2–1.35 (m, 1 H), 1.4–1.6 (m, 1 H), 2.42 (s, 3 H), 3.7–3.98 (m, 4 H), 7.32 and 7.76 (AB q, 4 H, J = 8.6 Hz); mass spectrum, m/e $M^{+\cdot}$ weak, 487, 445, 199 (base). Anal. Calcd for $C_{24}H_{46}O_5SSi_2$: C, 57.32; H, 9.22. Found: C, 57.08; H, 9.29.

2[*R*(*S*)],4[*S*(*R*)]-Bis[(*tert*-butyldimethylsilyl)oxy]-1-iodopentane (21d). I_2 (5.08 g) was added to Mg turnings (0.6 g) in Et_2O (37.5 mL) at 0 °C under nitrogen. The mixture was filtered to remove excess metal, the filtrate was added to **21c** (5.0 g) in Et_2O (15 mL), and the mixture was refluxed for 3 h. Aqueous $Na_2S_2O_3 \cdot 5H_2O$ was added, and the colorless ether layer was washed with water, dried, and evaporated to leave the iodide **21d** (3.2 g, 70%) as a clear liquid: IR 1470, 1260, 1080, 830 cm^{-1}; NMR (250 MHz) δ 0.02 (s, 12 H), 0.85 (s, 9 H), 0.88 (s, 9 H), 1.28 (d, 3 H, J = 6 Hz), 1.39–1.52 (m, 1 H), 2.2 (dt, 1 H, J = 12.2, 6.4 Hz), 3.7 (m, 2 H), 3.9–4.05 (m, 1 H), 4.35–4.45 (m, 1 H); mass spectrum, m/e $M^{+\cdot}$ absent, 399, 75 (base).

***tert*-Butyl 2-Methyl-3-oxobutanoate.** NaH (100%, 3.34 g) was added in portions to *tert*-butyl 3-oxobutanoate (20 g) in THF (100 mL) at 0 °C under nitrogen. When hydrogen evolution ceased, MeI (8.7 mL) was added, and the mixture was stirred overnight at room temperature. Filtration, evaporation, and distillation gave the title keto ester (18.4 g, 85%) as a colorless liquid: bp 66–67 °C (6 mmHg); IR 1730, 1455, 1370, 1150, 850 cm^{-1}; NMR (60 MHz) δ 1.25 (d, 3 H, J = 6.5 Hz), 1.45 (s, 9 H), 2.15 (s, 3 H), 3.3 (q, 1 H, J = 6.5 Hz); mass spectrum, m/e $M^{+\cdot}$ absent, 115, 57 (base). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.88; H, 9.51.

2[*S*(*R*)]-[2[*R*(*S*)]-Hydroxypropyl]oxirane (22a). 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.355 mL) was added to **21b** (0.65 g) in THF (25 mL) at 0 °C. After 24 h, ice, water, and Et_2O were

added. The aqueous phase was extracted with Et_2O, and the combined organic phases were dried and evaporated. Chromatography (CH_2Cl_2–Et_2O gradient 1:0–8:2) of the residue gave **22a** (0.11 g, 46%) as a clear liquid: IR 3420, 1410, 1370, 1260, 1140, 850, 830 cm^{-1}; NMR (60 MHz) δ 1.25 (d, 3 H, J = 6 Hz), 1.55–2.25 (m, 3 H), 2.35–3.35 (m, 3 H), 3.7–4.3 (m, 1 H); mass spectrum, m/e $M^{+\cdot}$ absent, 87, 58 (base). An aliquot of **22a** (50 mg) gave **22b** (0.10 g, 92%) on standard[29] *tert*-butyldimethylsilylation. Anal. Calcd for $C_{11}H_{24}O_2Si$: C, 61.05; H, 11.18. Found: C, 60.90; H, 11.45.

2-[2-[(*tert*-Butyldimethylsilyl)oxy]propyl]oxiranes (22b and 23b). The epoxide (**22a** and **22b**) mixture (3.6 g), from peracetic acid and 4-penten-2-ol,[21] was *tert*-butyldimethylsilylated.[29] Distillation of the crude product gave **22b** and **23b** (2.82 g, 37%) as an inseparable mixture: bp 92–95 °C (17 mmHg); IR 1460, 1260, 1220, 1090, 840, 770, 740, 670 cm^{-1}; NMR (60 MHz) δ 0.05 (s, 6 H), 0.85 (s, 9 H), 1.10 and 1.13 (2 d, 3 H, J = 6 Hz), 1.4–1.8 (m, 2 H), 2.3–3.15 (m, 3 H), 4.0 (m, 1 H); mass spectrum, m/e 215, 201, 183, 173, 159, 141, 127, 115, 101, 85 (base).

2,3[*R*(*S*)]-Dihydroxy-5[*S*(*R*)]-methyltetrahydrofuran (27a). Diisobutylaluminum hydride in PhMe (33% w/w, 30 mL) was diluted with PhMe (25 mL) at −78 °C under nitrogen and **16a** (3.1 g) added. After 2 h, HOAc (3.5 mL) was added over 30 min, and the mixture warmed up to 0 °C when water was added. The resultant precipitate was Soxholet extracted with EtOAc for 15 h. The combined filtrate and Soxholet extracts were evaporated to leave **27a** (1.97 g, 85%) as a colorless oil: IR 3400, 1720, 1450, 1390, 1260, 1060 cm^{-1}; NMR (60 MHz) δ 1.34 (d, 3 H, J = 7.0 Hz), 1.5–2.5 (m, 2 H), 3.85–4.55 (m, 2 H), 4.75 (br s, 2 H), 5.15–5.5 (m, 1 H); mass spectrum, m/e 118 ($M^{+\cdot}$), 83 (base). Benzoylation [PhCOCl (0.40 mL), pyridine (0.50 mL), and PhH (5 mL)] of an aliquot (0.20 g) gave the dibenzoate **27b** (0.40 g, 73%) as a colorless oil. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.98; H, 5.83.

5[*S*(*R*)]-[2[*S*(*R*)]-Hydroxypropyl]tetrahydrofuran-2-one (30a). [(Ethoxycarbonyl)methylene]triphenylphosphorane (**28**, 7.58 g) and lactol **27a** (2.5 g) in THF (50 mL) were stirred at room temperature for 14 h, refluxed for 3 h, cooled, and by using more THF filtered through Kieselgel (5 g). Rh on Al_2O_3 (5%, 1.0 g) was added to the filtrate and the mixture hydrogenated at atmospheric pressure for 15 h. The catalyst was filteed off through Celite, and the solids were extracted with more THF. The solution was evaporated and the residue partitioned between water and Et_2O. Evaporation of the aqueous layer gave an oil, which was dissolved in CH_2Cl_2 (40 mL) and CF_3CO_2H (1.0 mL) and refluxed for 6 h. Evaporation and distillation gave **30a** (1.84 g, 60%) as a colorless oil: bp 120 °C (0.35 mmHg); IR 3420, 1780, 1160 cm^{-1}; NMR (250 MHz) δ 1.26 (d, 3 H, J = 6 Hz), 1.7–2.0 (m, 4 H), 2.36 (ddd, 1 H, J = 13, 8, 6 Hz), 2.5–2.6 (m, 2 H), 4.03–4.13 (m, 1 H), 4.7–4.82 (m, 1 H); mass spectrum, m/e 144 ($M^{+\cdot}$), 126 (base). Reaction of an aliquot (60 mg) with *tert*-butylchlorodimethylsilane (66 mg), imidazole (71 mg), and DMF for 15 h at room temperature gave the silyl ether **30b** (90 mg, 84%) as a colorless oil: IR 1780, 1260, 1180, 1160, 1050, 1000 cm^{-1}; NMR (250 MHz) δ 0.08 (s, 6 H), 0.89 (s, 9 H), 1.16 (d, 3 H, J = 6.5 Hz), 1.64–1.72 (m, 2 H), 1.76–1.93 (m, 1 H), 2.28–2.41 (ddd, 1 H, J = 13, 8, 6 Hz), 2.49–2.56 (m, 2 H), 3.96–4.12 (m, 1 H), 4.62–4.72 (m, 1 H); ^{13}C NMR δ 177.0, 77.9, 65.3, 46.1, 28.7, 28.4, 25.8, 24.5, −4.3, −4.8; mass spectrum, m/e 260, 259, 201 (base). Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14. Found: C, 60.61; H, 10.26. As an alternative, the crude undistilled lactone **30a** was *tert*-butyldimethylsilylated and the product **30b** purified by chromatography (petroleum ether–CH_2Cl_2 gradient 1:0–0:1). In this way lactol **27a** (0.67 g) gave lactone **30b** (0.80 g, 55%).

2[*S*(*R*)]-[2[*S*(*R*)]-[(*tert*-Butyldimethylsilyl)oxy]propyl]-5(*E*)-[1-[(*tert*-butyloxy)carbonyl]ethylidene]tetrahydrofuran (31). Method A. *n*-Butyllithium (1.52 M, 11.47 mL) was added to diisopropylamine (2.7 mL) at 0 °C in THF (30 mL) under nitrogen. After 0.5 h the solution was cooled to −78 °C and *tert*-butyl propanoate (2.27 g) and, after 40 min, lactone **30b** (0.45 g) were added. The mixture was allowed to warm up to room temperature and stirred overnight. After cooling to 0 °C, HOAc (1.2 mL) was added and the solvent evaporated. The residue was partitioned between Et_2O and water, the ether layer was dried and evaporated, and the residue was chromatographed (petroleum ether–CH_2Cl_2 gradient 4:1–0:1) to give an oil (0.48 g). An aliquot (0.10 g) was dissolved in THF (10 mL) and refluxed for 8 h in the presence of Amberlite IR120H resin (0.20 g). Filtration, evaporation, and chromatography (petroleum ether–CH_2Cl_2 (1:0–1:1) gave **31** (87 mg, 64%) as a clear oil: IR 1690, 1638, 1365, 1305, 1255, 1110, 740 cm^{-1}; UV 246 nm (ϵ 13900); NMR (250 MHz) δ 0.07 (s, 6 H), 0.89 (s, 9 H), 1.17 (d, 3 H, J = 6.5 Hz), 1.47 (s, 9 H), 1.55–1.70 (m, 3 H), 1.77 (t, 3 H, J = 1 Hz), 2.1–2.23 (m, 1 H), 2.83–2.97 (m, 1 H), 3.07–3.23 (m, 1 H), 4.0–4.1 (m, 1 H), 4.42–4.54 (m, 1 H); mass spectrum, m/e 370 ($M^{+\cdot}$), 313, 297, 257, 57 (base). Anal. Calcd for $C_{20}H_{38}O_4Si$: C, 64.82; H, 10.33. Found: C, 64.58; H, 10.59.

Method B. The lactone **30b** (0.40 g) was condensed with *tert*-butyl 2-lithiopropanoate and the reaction quenched with HOAc. After evaporation, the residue was partitioned between Et_2O and water. The ether layer was dried and evaporated, and the residue was refluxed in THF (15 mL) with Amberlite IR120H resin (1.0 g) overnight. Filtration, evaporation, and chromatography gave **31** (0.43 g, 75%).

(±)-*tert*-Butyl 8-*O*-(*tert*-Butyldimethylsilyl)nonactate (32). The α,β-unsaturated ester **31** (88 mg) and Rh on Al_2O_3 (5%, 0.1 g) in THF (20 mL) were hydrogenated at 65 psi while the mixture was vigorously shaken. After 72 h, filtration, evaporation, and chromatography (petroleum ether–CH_2Cl_2 gradient 1:0–1:3) gave unreacted **31** (24 mg, 27%) and the nonactic acid derivative **32** (58 mg, 66%; 91% allowing for recovered **31**) as a colorless oil: IR 1735, 1460, 1365, 1260, 1150, 1060, 840, 780 cm^{-1}; NMR (250 MHz) δ 0.05 (s, 6 H), 0.88 (s, 9 H), 1.06 (d, 3 H, J = 7 Hz), 1.13 (d, 3 H, J = 6.5 Hz), 1.35 (s, 9 H), 1.5–1.6 (m, 4 H), 1.87–1.97 (m, 2 H), 2.34–2.45 (dq, 1 H, J = 8.5, 7 Hz), 3.85–4.10 (m, 3 H); the spectrum showed the presence of the minor diastereoisomer **33** with 1.05 (d, J = 7 Hz), 1.12 (d, J = 7 Hz), 1.34 (s); mass spectrum, m/e 299 ($M^{+\cdot}$ − *t*-BuO), 258 (base), 243, 217, 215, 203. Anal. Calcd for $C_{20}H_{40}O_4Si$: C, 64.47; H, 10.82. Found: C, 64.74; H, 11.02. The α,β-unsaturated ester **31** was inert to hydrogenation over 5% Rh on Al_2O_3, 10% Pd on carbon, or Adam's catalyst at 1 atm. Hydrogenation at 1000 psi over 5% Rh on Al_2O_3 in THF with or without $MgBr_2$ (1 equiv) proceeded with lower diastereoselection (1:1 and 2:1, respectively).

Reduction of Nonactin (1a). $LiAlH_4$ (20 mg) was added to nonactin (**1a**, 20 mg) in Et_2O (20 mL) at 0 °C under nitrogen. After 15 h, saturated aqueous Na_2SO_4 and anhydrous Na_2SO_4 were added, the solids filtered off, and the filtrate evaporated to leave diol **34** (19.5 mg, 95%) as a colorless oil: IR 3620, 3500, 1080, 1035 cm^{-1}; NMR (250 MHz) δ 0.85 (d, 3 H, J = 6.5 Hz), 1.21 (d, 3 H, J = 6.5 Hz), 1.26 (s, 1 H), 1.32 (s, 1 H), 1.5–1.8 (m, 5 H), 1.9–2.1 (m, 2 H), 3.57–3.72 (m, 3 H), 3.93–4.05 (m, 1 H), 4.05–4.18 (m, 1 H).

Reduction of the Synthetic Nonactic Acid Derivative 32. $LiAlH_4$ (10 mg) and **32** (73 mg) in Et_2O (15 mL) were stirred at room temperature for 24 h. After quenching with saturated aqueous Na_2SO_4, solid Na_2SO_4 was added. The solids were filtered off through Celite, and the solvent was evaporated to leave an oil (55 mg). The oil, KF (30 mg), CF_3CO_2H (0.2 mL), THF (5 mL), and H_2O (5 mL) were refluxed under nitrogen overnight. Evaporation and chromatography (CH_2Cl_2–EtOAc gradient 1:0–0:1) of the residue gave synthetic **34** (30 mg, 89%) as a colorless oil: IR identical with authentic **34**; NMR identical with **34** with the exception of additional peaks due to the minor diastereoisomer (**35**) at δ 0.95 (d, J = 6.5 Hz).

2,3[*R*(*S*)]-Dihydroxy-2-[[(*tert*-butyloxy)carbonyl]methyl]-5[*S*(*R*)]-methyltetrahydrofuran (36). *n*-BuLi (1.55 M, 36 mL) was added to diisopropylamine (7.8 mL) in THF (50 mL) at 0 °C under nitrogen. After 0.5 h, the solution was cooled to −78 °C, *tert*-butyl acetate (6.84 mL) was added, and the mixture stirred for 0.5 h. The acetoxy lactone **16a** (2.0 g) was added, and after 1 h the mixture was warmed up to room temperature and stirred overnight. After cooling to 0 °C, HOAc (3.2 mL) was added, the mixture evaporated, and the residue extracted with Et_2O. The extract was filtered and evaporated and the residue chromatographed (petroleum ether–CH_2Cl_2 gradient 1:1–1:3) to give *tert*-butyl 3-oxobutanoate (0.98 g) and **36** (1.86 g, 63%) as a yellow oil: IR 3450, 1720 cm^{-1}: NMR (60 MHz) δ 1.3 (d, 3 H, J = 6.0 Hz), 1.48 (s, 9 H), 1.75–2.50 (m, 1 H), 2.65 and 2.8 (2 s,

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2 H), 3.8–4.55 (m, 3 H); mass spectrum, m/e $M^{+\cdot}$ absent, 215, 159 (base). Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.85; H, 8.74.

[1*R*(*S*)]-5[*R*(*S*)]-Methoxy-7[*S*(*R*)]-methyl-2,6-dioxabicyclo[3.3.0]octan-3-one (37). CF_3CO_2H (0.5 mL) was added to **36** (0.25 g) in MeOH (9.5 mL) at 0 °C under nitrogen. After 1 h, evaporation and chromatography (petroleum ether–CH_2Cl_2 gradient 4:1–0:1) gave **37** (0.10 g, 54%) as a colorless oil: IR 1790 cm^{-1}; NMR (250 MHz) δ 1.34 (d, 3 H, J = 6.0 Hz), 1.74 (ddd, 1 H, J = 13.7, 8.2, 2.3 Hz), 2.55 (overlapping ddd as 5 lines, 1 H), 2.85 (AB q, 2 H, J = 16.4 Hz), 3.34 (s, 3 H), 4.32 (m, 1 H), 4.76 (dd, 1 H, J = 7.0, 2.3 Hz); mass spectrum, m/e 172 ($M^{+\cdot}$) 157, 141, 101 (base). Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.58; H, 7.27.

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Registry No. (±)-**1a**, 87598-04-7; **13b**, 87598-05-8; (±)-**14b**, 87598-06-9; (±)-**15a**, 87598-07-0; (±)-**15b**, 87598-08-1; (±)-**15c**, 87598-09-2; (±)-**16a**, 82242-81-7; (±)-**16b**, 87598-10-5; **17**, 41162-32-7; 18, 82242-80-6; (±)-**21a**, 13942-72-8; (±)-**21b**, 87598-11-6; (±)-**21c**, 87598-13-8; (±)-**21d**, 87598-12-7; (±)-**21e**, 87598-14-9; (±)-**22a**, 87678-04-4; (±)-**22b**, 87598-15-0; (±)-**23a**, 87678-05-5; (±)-**23b**, 87598-16-1; **27a**, 87678-06-6; **27b**, 87598-17-2; **28**, 1099-45-2; (±)-**30a**, 82242-83-9; (±)-**30b**, 82242-84-0; (±)-**31**, 82242-85-1; (±)-**32**, 82242-86-2; (±)-**33**, 82264-56-0; (±)-34, 58703-67-6; (±)-**35**, 87678-07-7; (±)-**36** (isomer), 87598-19-4; (±)-**36** (isomer 2), 87598-18-3; (±)-**37**, 87598-20-7; CH_3CHO, 75-07-0; di-*tert*-butyl oxalate, 691-64-5; *tert*-butyl acetate, 540-88-5; *tert*-butyl 3-oxobutanoate, 1694-31-1; *tert*-butyl (±)-2-methyl-3-oxobutanoate, 87598-21-8; *tert*-butyl propanoate, 20487-40-5.

A Chiral Recognition Model for the Chromatographic Resolution of N-Acylated 1-Aryl-1-aminoalkanes

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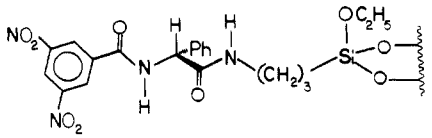
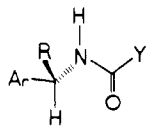
The enantiomers of *N*-acyl derivatives of 1-aryl-1-aminoalkanes generally may be chromatographically separated on a silica-bonded chiral stationary phase derived from *N*-(3,5-dinitrobenzoyl)phenylglycine. Chiral recognition is enhanced by increases in either the π basicity of the aryl substituent or the size of the alkyl substituent but is diminished by increases in the size of the acyl group. Carbamate and urea derivatives of these amines are also resolvable. Chiral recognition models are proposed to account for the observed chiral recognition and are used to assign absolute configuration to several acylated amines.

The enantiomers of a number of chiral amines can, as the α-naphthamide derivatives, be chromatographically separated on a silica-bonded chiral stationary phase.[1,2] Such separations provide the basis for sensitive and accurate determinations of enantiomeric purity and absolute configuration as well as a means of preparative resolution. The chiral stationary phase (CSP) employed, **1**, is derived



1

from (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine and is commercially available.[3,4] A variety of achiral acylating agents can be used to derivatize chiral amines to provide amides resolvable on **1**, α-naphthoyl chloride being used partly for its chromophoric properties. Amides of 1-aryl-1-aminoalkanes resolve particularly well on **1**. To gain insight into the modes of solute–CSP interaction that lead to chiral recognition, we have more closely examined the chromatographic resolution of *N*-acyl-1-aryl-1-aminoalkanes, **2**.



2, Y = alkyl, alkoxy, alkylamino

Table I presents representative data, including elution orders and the signs of $[\alpha]_D$, for the resolution of a series of type **2** amides on CSP **1**. Elution orders were established by chromatographing samples derived from enantiomerically enriched samples of configurationally known amines. Signs of $[\alpha]_D$ were obtained from a polarimetric detector used in tandem with an ultraviolet detector. Figure 1 illustrates a typical chromatogram. Preparative resolution of these amides is feasible, one such being described in the Experimental Section.

To summarize the data in Table I, an increase in either the π basicity of the aryl group or in the size of the alkyl substituent will enhance chiral recognition, whereas an increase in the length of the alkyl "tail" of the acyl group diminishes chiral recognition.[5] For all configurationally known compounds in Table I, the *S* enantiomers are last eluted from (*R*)-**1**.

The experimental observations may be rationalized by a chiral recognition model somewhat like that used to account[1] for the resolution on **1** of the α-naphthamides of amines of structure $R_1CHNH_2R_2$. Following our usual

(1) Pirkle, W. H.; Finn, J. M.; Hamper, B. C.; Hyun, M. H.; Schreiner, J. L.; Pribish, J.; Sowin, T. J.; Welch, C. J., paper presented at the Symposium on Molecular Interactions in Chemical Separations: Solutes, Solvents, and Surfaces, 184th ACS National Meeting, Kansas City, Missouri, Sept 1982.

(2) Pirkle, W. H., paper presented at the Midwest Regional Meeting of the Academy of Pharmaceutical Sciences, Chicago, Illinois, May 23, 1983.

(3) The column used is a commercial version (Regis Chemical Co.) of our earlier reported[4] CSP. Rather similar results can be obtained with the ionically bonded version of this CSP,[6] which is available from Regis and from J. T. Baker Chemical Co.

(4) Pirkle, W. H.; House, D. W.; Finn, J. M. *J. Chromatogr.* **1980**, *192*, 143.

(5) The extent of chiral recognition is gauged by the magnitude of α, the separability factor for the enantiomers.

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